

## Research Article



## Marine Sponges a Good Source of Bioactive Compounds in Anticancer Agents

P. Kamalakkannan\*

P.G. and Research Department of Zoology, Sir Theagaraya College, Chennai, India.

\*Corresponding author's E-mail: [drkamal781@gmail.com](mailto:drkamal781@gmail.com)

Accepted on: 12-02-2015; Finalized on: 31-03-2015.

### ABSTRACT

The development of more effective drugs for treating patients with cancer has been a major human endeavor over for more than 50 years, and now in the 21<sup>st</sup> century promises certain dramatic new directions. The potential of marine life as a source of novel molecules is immense. Marine organisms likely possess a greater molecular diversity than do their terrestrial counterparts. In comparison with the other, bioactive compounds have been detected especially frequently in sponges. Sponges (phylum: Porifera) are most primitive of the multicelled animals that have existed for 700–800 million years. Sponges produce a wide array of secondary metabolites ranging from derivatives of amino acids and nucleosides to terpenoids, macrolides, porphyrins, aliphatic cyclic peroxides and sterols. Of the investigated marine sponge species, >10% has exhibited cytotoxic activity suggesting production of potential medicinal. Potentially therapeutic compounds identified in sponges include immunomodulators and anticancer agents. Certain sponges seem to produce important and useful antifouling agents. The present study address pharmacological activities in marine sponges antitumor, antiviral, anti-inflammatory, immune or neuro suppressors, antimalarial, antibiotic and cytotoxic properties of 87 natural products (marine), most of the novel compounds that belongs to the family of porifera possessed the various species diverse structural classes, including steroids, terpenes, polyketides and peptides. The marine sponges continue to attract attention as rich sources of structurally novel anticancer secondary metabolites.

**Keywords:** Sponges, Porifera, anti-cancer, bioactive compounds, porphyrins, terpenes, steroids.

### INTRODUCTION

Marine environment is an exceptional reservoir of bioactive natural products, structural/chemical features not found in terrestrial natural products. Marine organisms have evolved biochemical and physiological mechanisms that include the production of bioactive compounds for such purposes as protection, communication, and reproduction against predation, infection and competition. Natural products have served as important chemical prototypes for the invention of new molecules, and continue to be the most important source of drug leads, especially in the anticancer field. In the last decades researchers of natural products chemistry focused their research in a wide variety of bioactive compounds from marine species. Marine sponges have been considered as a very fertile field for the discovery of bioactive natural chemical substances with respect to the diversity of their primary and secondary chemical components and metabolites. The new metabolites and its biological effects from sponges have been reported in a number of scientific research papers. Highly citation values and the reviews have been published in the last decades in relation to the sponge-derived chemicals with bioactive compounds which have the potential to be used for future pharmaceutical applications.<sup>1-4</sup>

Marine sponges have been the largest source of new marine natural products being reported annually and they have been furnishing structurally diverse bioactive compounds for the new-drug discovery programme. Some of these include discodermolide and natural

product analogue cytosine arabinoside from the Caribbean sponge *Discodermia dissolute* and *Tethyacrypta*, respectively, agelasphin from *Agelas mauritianus* and halichondrin B from the Japanese sponge *Halichondria kadai*.<sup>5,6</sup>

### Marine Sponges as Pharmacy

Pharmaceutical interest in sponges was aroused in the early 1950's by the discovery of a number of unknown nucleosides: spongothymidine and spongouridine in the marine sponge *Cryptotheca crypta*.<sup>7,8</sup> But now, nearly more than 15,000 products of marine species have been described. Marine sponges are champion producers, concerning the products diversity has been found stated that sponges are responsible for more than 5300 different products and every year hundreds of new compounds are being discovered.<sup>9-11</sup>

Most bioactive compounds from sponges can be classified as anti-inflammatory, antitumour, antibiotic or antifouling, antiviral, antimalarial, and immune or neurosuppressive. The products of sponges and its chemical diversity are remarkable<sup>12</sup> have been explained that the unusual nucleosides, sterols, bioactive terpenes, alkaloids, fatty acids, peroxides, cyclic peptides, and amino acid derivatives (which are frequently halogenated) have been described from sponges.

Marine sponges have a potential to provide future drugs against important diseases, such as malaria, cancer and a range of viral diseases.<sup>13</sup> Of 10,000 marine sponges, 11 genera are known to produce bioactive compounds, and only three genera (*Haliclona*, *Petrosia* and *Discodermia*)



are known to produce anticancer, anti-malarial, and anti-inflammatory compounds. The marine sponges are rich sources of structurally novel bioactive secondary metabolites.

In this review we have focused on the pharmacologically active marine natural products that have been shown to have biological activity including cytotoxic and anticancer activities for potential drug applications in marine sponges.

### Production of Bioactive Compounds

Marine animals in general and marine invertebrates in particular are promising organisms for novel bioactive compounds synthesis.<sup>14</sup> Explained that this is an adaptation to thrive in the extreme environmental conditions of the sea and as a defense strategy to escape from predators by the marine invertebrates especially soft bodied animals like sponges.

Focusing on sponges, a conceptual progress occurred with the study of<sup>15</sup> suggested that marine animals and their symbiotic microorganisms (bacteria and fungi) produce an array of bioactive compounds against foreign attackers. The recent concept is the notion that environmental biotic constraints driven that symbiosis. The host (sponge) synthesizes bioactive compounds that provide protection against attacking microorganisms or eukaryotes, e.g., acetylenic compounds<sup>16</sup>. The symbiotic bacteria or fungi produce secondary metabolites that act as antibiotics, e.g., cribrastatin<sup>17</sup>, or as cytostatic agents, e.g. sorbicillactone-A.<sup>18</sup> Functionally, these compounds act only as defense molecules. Another functional class of secondary metabolites of sponges and their associated microorganisms play a dual role: they are involved in defense as well as in the activation of pathways crucial for self defense.<sup>14</sup> The sponges possess molecules similar to and homologous with those of the innate and adaptive immune systems of higher metazoan.

### Marine Sponges and Anti Cancer Compounds

A number of isolated sponge compounds are inhibitors of protein kinase C (PKC). PKC inhibitors have attracted interest worldwide, as there is evidence that too high levels of PKC enzyme are involved both in the pathogenesis of arthritis and psoriasis (owing to regulation of phospholipase A2 activity), and in tumor development.<sup>19,20</sup> PKC is believed to be the receptor protein of tumor-promoting PKC inhibitors and phorbol esters that prevent carcinosarcoma cells binding to the endothelium. Springer and Lasky, 1991 studied that glycosylation of the receptors, and especially the presence of fructose residues, plays an important role in the binding of carcinosarcoma cells and leukocytes to the receptors in the endothelium.

In the last few years there are several other candidates from marine natural compounds in the pipeline for evaluation in Phase I–III clinical trials for the treatment of various cancers.<sup>21</sup> A review in 2003 collected the most

important marine natural compounds which were undergoing preclinical and clinical trials (I, II, III) for anticancer activity.<sup>22</sup> explained that the compounds from sponges were the following: Discodermolide, modified halichondrin B, KRN-70000, Hemiasterlins A & B, Fascaphysins (alkaloid), Halichondrin B, Alipkinidine (alkaloid), Isohomahalichondrin B, 5-methoxyamphimedine (alkaloid), Laulimalide/Fijianolide and Variolin (alkaloid).

One natural compound from marine sponges with promising anticancer activity is Renieramycin M. They are members of the tetrahydroiso-quinoline family that were isolated from marine sponges belonging to genera *Reniera*. The pre-clinical results reveal that Renieramycin M induced cancer cells in lungs, apoptosis through p53-dependent pathway and the compound may inhibit progression and metastasis of lung cancer cells.<sup>21</sup> (Figure 1).

Monanchocidin is a novel polycyclic guanidine alkaloid isolated from the marine sponge *Monanchora pulchra* that induced cell death in human monocytic leukemia (THP-1), human cervical cancer (HeLa) and mouse epidermal (JB6 Cl41) cells.<sup>22</sup> (Figure 2) Smenospongine, is a sesquiterpene aminoquinone, obtained from the *Smenospongia* sp. sponges and demonstrated that Smenospongine induces antiangiogenic activities, antimicrobial, antiproliferative and cytotoxic.<sup>23</sup> (Figure 3).

The macrocyclic lactone polyether Spongistatin-I was isolated as in 1993 from the marine sponge *Spongia* sp.<sup>26</sup> Spongistatin-I was shown to mitosis inhibition, assembly of microtubule and the vinblastine binding to tubulin thereby inducing cytotoxic cell death in numerous cancer cell lines.<sup>24</sup> (Figure 4).

Another component from sponges that attracted the interest of scientists as an antitumor agent was Heteronemin, isolation of a marine sesterterpene from the sponge *Hyrtios* sp., particularly for its biological effects on chronic myelogenous leukemia cells. The results explained that Heteronemin affecting the cellular processes including apoptosis, cell cycle, MAPKs pathway (mitogen-activated protein kinases) and the nuclear factor kappa B (NF-kappaB) signaling cascade. The compound having potential as anti-inflammatory and anti-cancer agents.<sup>25</sup> (Figure 5).

Manzamine A, a beta-carboline alkaloid present in several marine sponge species, has potent anti-inflammatory activity, antifungal, anti-HIV-I activities with moderate antitumor activities.<sup>26</sup> Oral and intravenous pharmacokinetic studies of manzamine A derivatives in rats indicated that they have metabolic clearance in low level, a reasonably pharmacokinetic half life is long, and good absolute oral bioavailability which make them as potential leads for preclinical assessment. In addition, 8-hydroxymanzamine A, isolated from an undescribed sponge, *Pachypellina* species exhibited moderate antitumor and anti HSV-II activity (Figure 6).



## CONCLUSION

Marine invertebrates are one of the major groups of biological organisms now that gave significant number of natural products and secondary metabolites with pharmacological properties and led in the formulation of novel drugs. The rich diversity in bioactive compounds from sponges has provided molecules that interfere with the pathogenesis of a disease at many different points, which increase the chances of developing selective drugs against specific targets. Marine sponges have provided many examples of novel secondary metabolites that possess varied chemical status and potential cancer activity. Marine natural products provide a novel and rich source of chemical diversity that can contribute to design and development of new and potentially useful anticancer agents. Unfortunately, these secondary

metabolites are usually present in natural stocks and trace amounts and are too small for sustaining the development of widely available and useful medicines. That helps to obtain more quantities of the secondary metabolites is therefore currently the most important quest. The current metabolite is to study the feasibility of pharmaceuticals from sponges at a large-scale.

The available data demonstrates that the marine ecosystem is not only productive to discover anticancer entities but it is also a tool to identify new cellular targets for therapeutic intervention. A better understanding of the molecular determinants of therapeutic response will help identify patients at risk for severe toxicities or those more likely to respond to a given therapeutic regimen, thus paving the way for customized anticancer activity to become a reality in the near future.

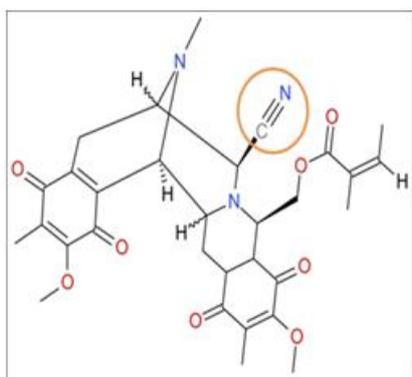


Figure 1: Structure of Renieramycin M

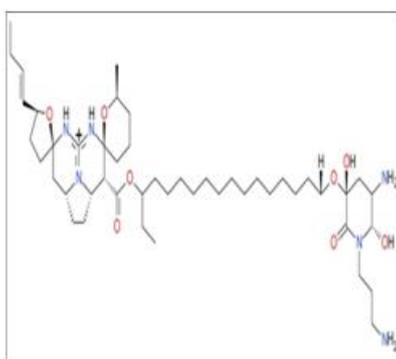


Figure 2: Structure of Monanchocidin

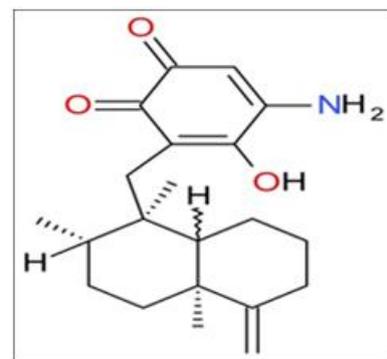


Figure 3: Structure of Smenospongine

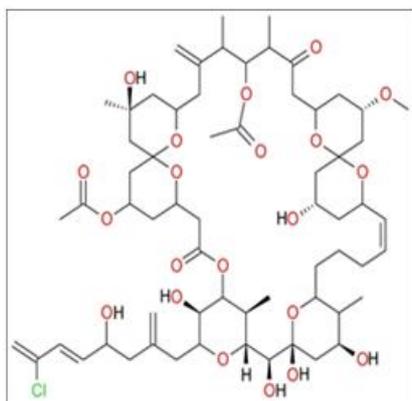


Figure 4: Structure of Spongistatin 1

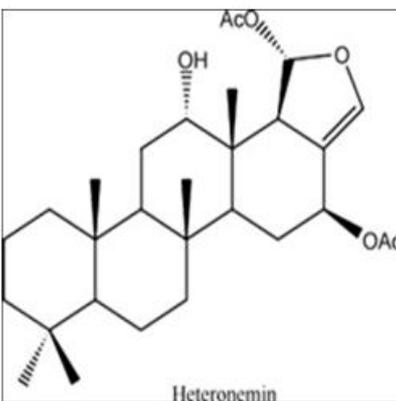


Figure 5: Structure of Heteronemin

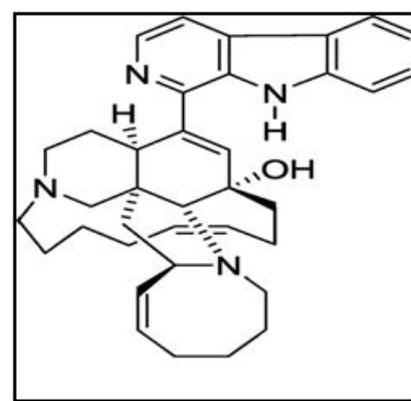


Figure 6: Structure of Manzamine

## REFERENCES

- Higa T, Tanak J, Kitamura A, Koyama T, M. Takahash, Bioactive compounds from marine sponges. *Pur and Appl Chem*, 66, 1994, 2227-2230.
- Haefner B, Drugs from the deep: marine natural products as drug candidates. *Drug Discovery Today*, 8, 2003, 536-544.
- Belarbi H, Contreras Gómez A, Chisti Y, García Camacho F, E. Molina Grima, Producing drugs from marine sponges. *Biotech Adv*, 21, 2003, 585-598.
- Sipkema D, Franssen MC, Osinga R, Tramper J, R.H. Wijffels, Marine sponges as pharmacy. *Mar Biotech (NY)*, 7, 2005, 142-162.
- Bergmann W., R.J. Feeney, The isolation of a new thymine pentoside from sponges. *J Ameri Chem Soc*, 72, 1950, 2809-2810.
- Bergmann, W., R.J. Feeney, 1951. Contributions to the study of marine products. XXXII The nucleosides of sponges. *Int J Org Chemi*, 16, 1951, 981-987.
- Faulkner, D.J Marine natural products. *Nat Prod Rep*, 17, 2000, 7-55.

8. Faulkner, D.J Marine natural products. Nat Prod Rep, 18, 2001, 1-49.
9. Faulkner, D.J Marine natural products. Nat Prod Rep, 19, 2002, 1-48.
10. Tramper j, Cultivation of Marine Sponges. Detmer Sipkema. Process Engineering Group, Wageningen University, The Netherlands. 1999, 184.
11. Abel Aneiros, Anoland Garateix, Bioactive peptides from marine sources: pharmacological properties and isolation procedures. J Chromato, 803, 2004, 41-53.
12. Werner E.G Müller , Heinz C Schröder, Matthias Wiens, Sanja Perovic-Ottstadt, Renato Batel, and Isabel M Müller, Traditional and Modern Biomedical Prospecting: Part II—the Benefits Approaches for a Sustainable Exploitation of Biodiversity (Secondary Metabolites and Biomaterials from Sponges), Adnc Acc Pub, 1(2), 2004, 133–144.
13. Thakur N.L., Hentschel U., Krasko A., Anil A.C., and W.E.G. Müller, Antibacterial activity of the sponge *Suberites domuncula* and its primmorphs: potential basis for chemical defense. Aquac Micro Ecol, 31, 2003, 77–83.
14. Richelle-Maurer E., Gomez R., Braekman J.C, Van de Vyver G., Van Soest R.W.M., and C. Devijver, Primary cultures from the marine sponge *Xestospongia muta* (Petrosiidae, Haplosclerida). J Biotech, 100, 2003, 169–176.
15. Pettit G.R., Knight J.C., Collins J.C., Herald D.L., and V.G. Young, Antineoplastic agent 430 isolation and structure of cribostatins 3, 4 and 5 from the Republic of Maldives *Cribrachalina* sp. J Natl Prod, 63, 2000, 793–798.
16. Bringmaan G., Lang G., Muchlbacher J and K. Schaumaan, A structurally unprecedented bioactive novel type alkaloid from a sponge derived fungus. In Marine Molecular Biotechnology, WEG Muller (Ed) Springer-Press, Berlin, 2003, 231-251.
17. Bradshaw HD, Villar M, Watson BD, Otto KG, Stewart S, Stettler RF, Molecular genetics of growth and development in *Populus*. III. A genetic linkage map of a hybrid poplar composed of RFLP, STS, and RAPD markers. Theor Appl Genet, 89, 1994, 167–178.
18. Yoshiji H, Harris SR, Raso E, Gomez DE, Lindsay CK, Shibuya M, Sinha CC and Thorgeirsson UP. Int J Canc, 75, 1998, 81-87.
19. Mayer A.M.S., Rodríguez A.D., Tagliatalata-Scafati O., and F. Fusetani, Marine Pharmacology in 2009–2011: Marine Compounds with Antibacterial, Antidiabetic, Antifungal, Anti-Inflammatory, Antiprotozoal, Antituberculosis, and Antiviral Activities; Affecting the Immune and Nervous Systems, and other Miscellaneous Mechanisms of Action. Mar Drug, 11, 2013, 2510-2573.
20. Crews P, Gewick W.H, Schmitz F.J, France D, and B.W.K. Bai, Molecular approaches to discover marine natural products anticancer leads-An update from drug discovery group collaboration. Pharmac Bio, 41, 2003, 39-52.
21. Halim H, Chunhacha P, Suwanborirux K, and P. Chanvorachote, Anticancer and antimetastatic activities of Renieramycin M, a marine tetrahydroisoquinoline alkaloid, in human non-small cell lung cancer cells. Anticancer Res, 31, 2011, 193-201.
22. Guzui A.G, Makarieva T.N, Denisenko V.A, Dmitrenko P.S, Kuzmich A.S. Monanchocidin: a new apoptosis-inducing polycyclic guanidine alkaloid from the marine sponge *Monanchora pulchra*. Org Lett, 12, 2010, 4292-4295.
23. Kondracki M.L, and M. Guyot, Smenospongine: a cytotoxic and antimicrobial aminoquinone isolated from smenospongia. Tetrah Lett, 27, 1987, 5815-5818.
24. Bai R, Cichacz Z.A, Herald C.L, Pettit G.R, and E. Hamel, Spongistatin 1, a highly cytotoxic, sponge-derived, marine natural product that inhibits mitosis, microtubule assembly, and the binding of vinblastine to tubulin. Mol Pharma, 44, 1993, 757-766.
25. Rabelo L, Monteiro N, Serquiz R, Santos P, Oliveira R, A lactose-binding lectin from the marine sponge *Cinachyrella apion* (Cal) induces cell death in human cervical adenocarcinoma cells. Mar Drug, 10, 2012, 727-743.
26. Faircloth J. B., Capella L. M., and B.L. Alford, The effect of brand attitude and brand image on brand equity. J Mark Theo and Prac, 9(3), 2001, 61–74.

**Source of Support:** Nil, **Conflict of Interest:** None.

#### Corresponding Author's Biography: Dr. P. Kamalakkannan



Dr. P. Kamalakkannan graduated and post-graduated from Jamal Mohammed College, Trichy, Tamil Nadu. During his post-graduation, he had a project titled "A study on Pollution Sensitiveness of a fish *Channa punctatus*". He had his M.Phil., too at Jamal Mohammed College, with a dissertation titled "Microbial Potential in Bioremediation of Tannery effluent". He was awarded Ph.D., at Presidency College, Chennai (affiliated to the University of Madras) for his dissertation titled "Characterizations and Impact of Tannery effluents on the biochemical, histopathological and molecular changes in various tissues if a fish, *Channa punctatus*". With a flair for teaching, he started his career by teaching Post Graduate students at Bharathidasan University, Trichy. After serving for one year, he migrated to Sir Theagaraya College, Chennai, and has been serving as Assistant Professor in the PG and Research Department of Zoology and Bio-technology for the last two years.